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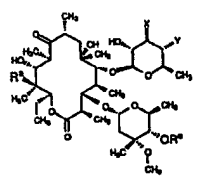
(54) Title: USE OF MACROLIDES FOR THE TREATMENT OF CANCER AND MACULAR DEGENERATION

(57) Abstract

A method for treating tumors and macular degeneration in a human or veterinary patient comprising administering a compound selected from the group consisting of (I), (II), (III), (IV), (V), (VI), (VII), and a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound thereof.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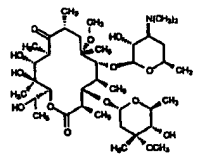
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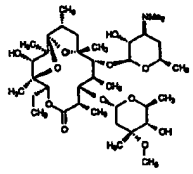
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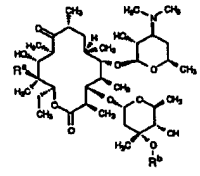
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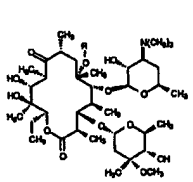
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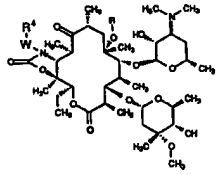
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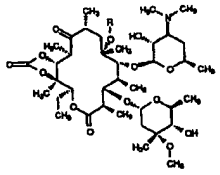
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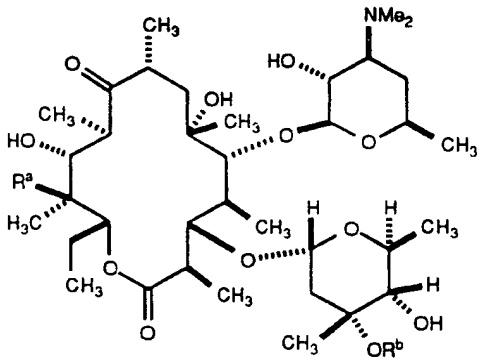
Use of Macrolides for the Treatment of Cancer and Macular Degeneration

Technical Field

The present invention relates to novel utilities of semi-synthetic macrolides, specifically antitumor activity and activity against macular degeneration. More particularly, the invention relates to the use of 6-O-substituted erythromycin derivatives and compositions containing such compounds for the treatment of tumors and macular degeneration.

Background of the Invention

Erythromycins A through D, represented by formula (E), are well-known and



(E)

Erythromycin	R^a	R^b
A	-OH	$-CH_3$
B	-H	$-CH_3$
C	-OH	-H
D	-H	-H

potent antibacterial agents. However, reports have appeared over the past few years which suggest that Erythromycin may possess antitumor as well as other beneficial activities.

Hamada *et al.* have reported that tumor bearing mice treated with oral erythromycin at doses of 1-10 mg/kg had a two- to three-fold increase in survival times compared to control mice (*Chemotherapy*, 41, 59-69 (**1995**)). Mikasa *et al.* reported that long-term clarithromycin treatment of lung cancer patients prolonged survival time (*Chemotherapy*, 43, 288-296 (**1997**)). WO 95/28939 discloses that 14- or 15-membered macrolide compounds, including clarithromycin and erythromycin B, have a potent antitumor effect on non-small cell lung cancers and are therefore useful as practical therapeutic agents for this type of cancer. These tumors are considered the most difficult to treat with surgery or chemotherapy.

Much research and many resources have been devoted to the development of antitumor drugs, and some successful chemotherapeutic agents have been developed. However, new

antitumor agents and methods for inhibiting, remitting, or controlling growth of tumors are still needed.

Angiogenesis is the process by which new blood vessels invade a tissue. This occurs normally during wound healing, menstruation and development of an embryo. However, angiogenesis is very important in the development of some tumors. This process of generating new capillary blood vessels, also referred to as neovascularization, is an essential feature of fibroproliferative processes representing solid tumor growth and inflammation. Numerous reviews of this subject exist, however, and that by Phillips *et al.* (*Int. J. Cancer*, 17, 549-588 (**1976**) is a useful introduction to the subject.

Unlike angiogenesis in normal physiological situations, tumor-induced angiogenesis continues indefinitely until the cancer kills the host or unless the tumor is eradicated. Therefore, inhibition of the angiogenic process would be expected to slow the growth of some solid tumors. Marshall and Hawkins have reviewed the clinical experience with anti-angiogenic compounds in the treatment of both malignant and benign disease (*Breast Cancer Research and Treatment*, 36, 253-261 (**1995**)).

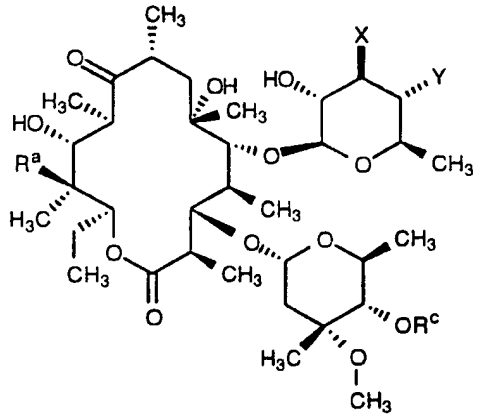
The pathological growth of new blood vessels also underlies most eye diseases that cause catastrophic loss of vision. These new vessels -- which proliferate under the sensory retina -- leak serum and blood, which in turn leads to a fibrotic reaction or disciform scar. When left untreated, choroidal neovascularization generally results in severe visual loss in 50% to 90% of the affected eye. Additionally, patients with a neovascular membrane in one eye are at substantial risk of a neovascular membrane in the second eye within 5 years. Therefore, patients with macular degeneration must be treated with antiangiogenic agents before extensive neovascularization and permanent scarring have occurred.

Age-related macular degeneration (AMD) is the most common cause of visual loss in elderly Americans. Choroidal neovascularization associated with severe visual loss will develop in 10-20% of patients with age-related macular degeneration. Current treatments for age-related macular degeneration fall into four categories: subretinal surgery, laser surgery, radiation, and pharmacological therapies. No satisfactory pharmacological treatment exists for choroidal neovascularization or age-related macular degeneration. Antiangiogenic agents are among the latest compounds to be used for the pharmacological treatment of macular degeneration. These antiangiogenic drugs are useful in treating the neovascular phase of this disorder. Antiangiogenic therapy primarily inhibits the growth of new vessels, rather than promoting regression of existing vessels. Therefore, there exists a need for agents that could prevent the development, growth or recurrence of these medical conditions.

The present invention provides new utilities of semi-synthetic 6-O-alkyl erythromycin derivatives, specifically for the treatment of tumors and macular degeneration.

Summary of the Invention

The present invention provides a method of treating tumors and macular degeneration in a human or veterinary patient comprising administering to a patient a therapeutically effective amount of a compound selected from the group consisting of:



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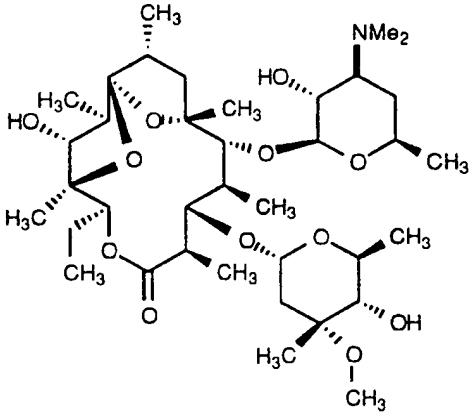

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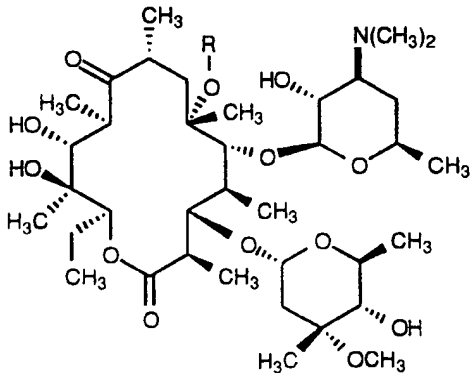

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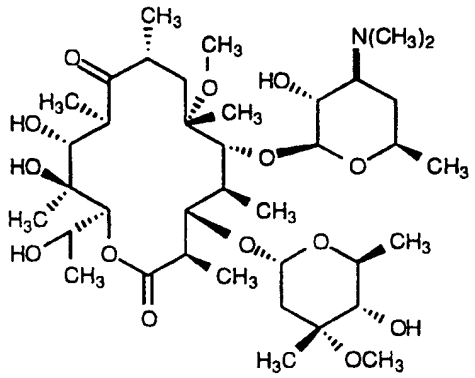

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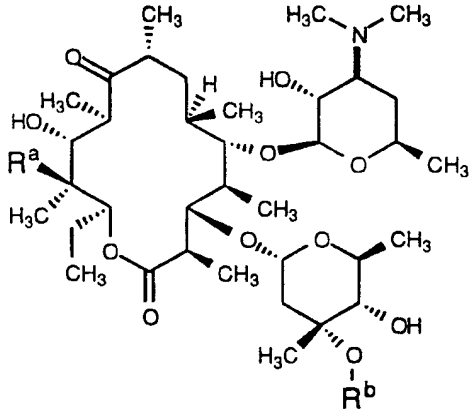

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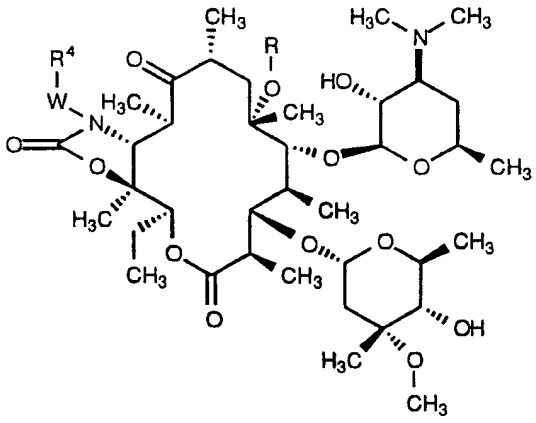
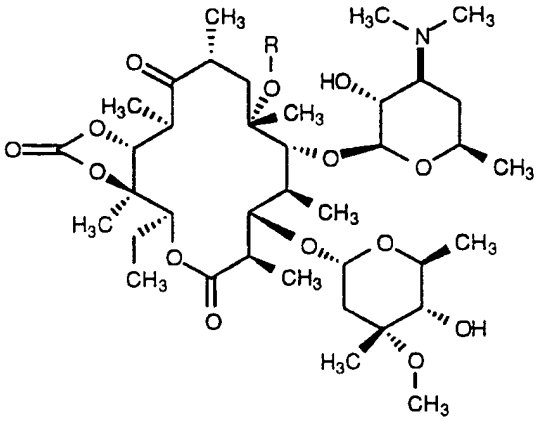


, and



(VII),

wherein

R^a is hydrogen or hydroxy;

R^b is hydrogen or methyl;

R^c is hydrogen or hydroxy protecting group;

X is $-NR^1R^2$, wherein R^1 and R^2 are independently selected from

(1) hydrogen, and

(2) C_1-C_3-alkyl optionally substituted with a substituent selected from the group consisting of

(a) aryl,

(b) substituted-aryl,

(c) heteroaryl, and

(d) substituted-heteroaryl,

Y is hydrogen or hydroxyl;

or

X and Y taken together form a bond;

W is absent or is selected from the group consisting of -O-, -NH-, -NH-CO-, and -N=CH;

R^w is selected from the group consisting of

(1) hydrogen,

(2) C_1-C_6-alkyl optionally substituted with one or more substituents selected from the group consisting of

(a) aryl,

(b) substituted-aryl,

(c) heteroaryl,

(d) substituted-heteroaryl,

(e) hydroxy,

(f) C_1-C_6-alkoxy,

(g) NR^1R^2, wherein R^1 and R^2 are as defined previously,

and

(h) $-CH_2-M-R^3$

wherein M is selected from the group consisting of:

(i) -C(O)-NH-,
(ii) -NH-C(O)-,
(iii) -NH-,
(iv) -N=,
(v) $-N(CH_3)-$,
(vi) -NH-C(O)-O-
(vii) -NH-C(O)-NH-
(viii) -O-C(O)-NH-
(ix) -O-C(O)-O-
(x) -O-,
(xi) $-S(O)_n-$, wherein n is 0, 1 or 2,
(xii) -C(O)-O-,
(xiii) -O-C(O)-, and
(xiv) -C(O)-,

and

R^3 is selected from the group consisting of:

(i) C_1-C_6-alkyl, optionally substituted with a substituent selected from the group consisting of
(aa) aryl,
(bb) substituted-aryl,
(cc) heteroaryl, and
(dd) substituted-heteroaryl,
(ii) aryl,
(iii) substituted-aryl,
(iv) heteroaryl,
(v) substituted-heteroaryl, and
(vi) heterocycloalkyl,

(3) C_3-C_7-cycloalkyl,
(4) aryl,
(5) substituted-aryl,
(6) heteroaryl, and
(7) substituted-heteroaryl;

R is selected from the group consisting of

(1) methyl substituted with a moiety selected from the group consisting of

(a) CN,

(b) F,

(c) $-CO_2R^4$ wherein R^4 is selected from the group consisting of C_1-C_3-alkyl, aryl substituted C_1-C_3-alkyl, and heteroaryl substituted C_1-C_3-alkyl,

(d) $S(O)_nR^4$ where n is 0, 1 or 2 and R^4 is as previously defined,

(e) $NHC(O)R^4$ where R^4 is as previously defined,

(f) $NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,

(g) aryl,

(h) substituted aryl,

(i) heteroaryl, and

(j) substituted heteroaryl;

(2) C_2-C_{10}-alkyl;

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) C_1-C_3-alkoxy-C_1-C_3-alkoxy,

(e) oxo,

(f) $-N_3$,

(g) -CHO,

(h) $O-SO_2-$(substituted C_1-C_6-alkyl),

(i) $-NR^5R^6$ wherein R^5 and R^6 are selected from the group consisting of

(i) hydrogen,

(ii) C_1-C_{12}-alkyl,

(iii) substituted C_1-C_{12}-alkyl,

(iv) C_1-C_{12}-alkenyl,

(v) substituted C_1-C_{12}-alkenyl,

(vi) C_1-C_{12}-alkynyl,

(vii) substituted C_1-C_{12}-alkynyl,

(viii) aryl,

(ix) C_3-C_8-cycloalkyl,

(x) substituted C_3-C_8-cycloalkyl,

(xi) substituted aryl,

(xii) heterocycloalkyl,
(xiii) substituted heterocycloalkyl,
(xiv) C_1-C_{12}-alkyl substituted with aryl,
(xv) C_1-C_{12}-alkyl substituted with substituted aryl,
(xvi) C_1-C_{12}-alkyl substituted with heterocycloalkyl,
(xvii) C_1-C_{12}-alkyl substituted with substituted heterocycloalkyl,
(xviii) C_1-C_{12}-alkyl substituted with C_3-C_8-cycloalkyl,
(xix) C_1-C_{12}-alkyl substituted with substituted C_3-C_8-cycloalkyl,
(xx) heteroaryl,
(xxi) substituted heteroaryl,
(xxii) C_1-C_{12}-alkyl substituted with heteroaryl, and
(xxiii) C_1-C_{12}-alkyl substituted with substituted heteroaryl,

or

R^5 and R^6 are taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring which may be substituted with one or more substituents independently selected from the group consisting of

(aa) halogen,
(bb) hydroxy,
(cc) C_1-C_3-alkoxy,
(dd) C_1-C_3-alkoxy-C_1-C_3-alkoxy,
(ee) oxo,
(ff) C_1-C_3-alkyl,
(gg) halo-C_1-C_3-alkyl, and
(hh) C_1-C_3-alkoxy-C_1-C_3-alkyl,

(j) $-CO_2R^4$ wherein R^4 is as previously defined,
(k) $-C(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,
(l) $=N-O-R^4$ wherein R^4 is as previously defined,
(m) -CN,
(n) $O-S(O)_nR^4$ wherein n is 0, 1 or 2 and R^4 is as previously defined,
(o) aryl,
(p) substituted aryl,
(q) heteroaryl,
(r) substituted heteroaryl,
(s) C_3-C_8-cycloalkyl,
(t) substituted C_3-C_8-cycloalkyl,
(u) C_1-C_{12}-alkyl substituted with heteroaryl,

(v) heterocycloalkyl,

(w) substituted heterocycloalkyl,

(x) $NHC(O)R^4$ where R^4 is as previously defined,

(y) $NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,

(z) $=N\text{-}NR^5R^6$ wherein R^5 and R^6 are as previously defined,

(aa) $=N\text{-}R^3$ wherein R^4 is as previously defined,

(bb) $=N\text{-}NHC(O)R^4$ wherein R^4 is as previously defined,

and

(cc) $=N\text{-}NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined;

(4) C_3-alkenyl substituted with a moiety selected from the group consisting of

(a) halogen,

(b) -CHO,

(c) $-CO_2R^4$ where R^4 is as previously defined,

(d) $-C(O)\text{-}R^3$ where R^3 is as previously defined,

(e) $-C(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,

(f) -CN,

(g) aryl,

(h) substituted aryl,

(i) heteroaryl,

(j) substituted heteroaryl,

(k) C_3-C_7-cycloalkyl,

and

(l) C_1-C_{12}-alkyl substituted with heteroaryl,

(5) C_4-C_{10}-alkenyl;

(6) C_4-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of

(a) halogen,

(b) C_1-C_3-alkoxy,

(c) oxo,

(d) -CHO,

(e) $-CO_2R^4$ where R^4 is as previously defined,

(f) $-C(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,

(g) $-NR^5R^6$ wherein R^5 and R^6 are as previously defined,

(h) $=N\text{-}O\text{-}R^4$ where R^4 is as previously defined,

(i) -CN,

(j) $O\text{-}S(O)_nR^4$ where n is 0, 1 or 2 and R^4 is as previously defined,

(k) aryl,
(l) substituted aryl,
(m) heteroaryl,
(n) substituted heteroaryl,
(o) C_3-C_7-cycloalkyl,
(p) C_1-C_{12}-alkyl substituted with heteroaryl,
(q) $NHC(O)R^4$ where R^4 is as previously defined,
(r) $NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,
(s) $=N\text{-}NR^5R^6$ wherein R^5 and R^6 are as previously defined,
(t) $=N\text{-}R^3$ wherein R^3 is as previously defined,
(u) $=N\text{-}NHC(O)R^4$ where R^4 is as previously defined,
and
(v) $=N\text{-}NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined;

(7) C_3-C_{10}-alkynyl;
and
(8) C_3-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of
(a) trialkylsilyl,
(b) aryl,
(c) substituted aryl,
(d) heteroaryl,
and
(e) substituted heteroaryl.

The present invention also provides pharmaceutical compositions for treating tumors and macular degeneration in a human or veterinary patient comprising a pharmaceutically acceptable carrier and a compound selected from formulas (I) - (VII) above in combination with a pharmaceutically acceptable carrier.

Detailed Description of the Invention

Definitions

As used throughout this specification and the appended claims, the following terms have the meanings specified.

The terms "C_1-C_3-alkyl", "C_1-C_6-alkyl", and "C_1-C_{12}-alkyl" as used herein refer to saturated, straight- or branched-chain hydrocarbon radicals derived from a hydrocarbon moiety containing between one and three, one and six, and one and twelve carbon atoms, respectively,

by removal of a single hydrogen atom. Examples of C_1-C_3-alkyl radicals include methyl, ethyl, propyl and isopropyl. examples of C_1-C_6-alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl and n-hexyl. Examples of C_1-C_{12}-alkyl radicals include, but are not limited to, all the foregoing examples as well as n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl and n-docecyl.

The term "C_1-C_6-alkoxy" as used herein refers to an C_1-C_6-alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. Examples of C_1-C_6-alkoxy, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *tert*-butoxy, neopentoxy and n-hexoxy.

The term "C_1-C_{12}-alkenyl" denotes a monovalent group derived from a hydrocarbon moiety containing from two to twelve carbon atoms and having at least one carbon-carbon double bond by the removal of a single hydrogen atom. Alkenyl groups include, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, and the like.

The term "C_1-C_{12}-alkynyl" as used herein refers to a monovalent group derived from a hydrocarbon containing from two to twelve carbon atoms and having at least one carbon-carbon triple bond by the removal of a single hydrogen atom. Representative alkynyl groups include ethynyl, 2-propynyl (propargyl), 1-propynyl and the like.

The term "alkylene" denotes a divalent group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2-dimethylpropylene, and the like.

The term "C_1-C_3-alkylamino" as used herein refers to one or two C_1-C_3-alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. Examples of C_1-C_3-alkylamino include, but are not limited to methylamino, dimethylamino, ethylamino, diethylamino, and propylamino.

The term "oxo" denotes a group wherein two hydrogen atoms on a single carbon atom in an alkyl group as defined above are replaced with a single oxygen atom (i.e. a carbonyl group).

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, substituted loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, acylamino, cyano, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "C_3-C_{12}-cycloalkyl" denotes a monovalent group derived from a monocyclic or bicyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom.

Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, and bicyclo[2.2.2]octyl.

The terms "halo" and "halogen" as used herein refer to an atom selected from fluorine, chlorine, bromine and iodine.

The term "alkylamino" refers to a group having the structure -NHR' wherein R' is alkyl, as previously defined. Examples of alkylamino include methylamino, ethylamino, *iso*-propylamino and the like.

The term "dialkylamino" refers to a group having the structure -NR'R" wherein R' and R" are independently selected from alkyl, as previously defined. Additionally, R' and R" taken together may optionally be $-(CH_2)_k-$ where k is an integer of from 2 to 6. Examples of dialkylamino include, dimethylamino, diethylaminocarbonyl, methylethylamino, piperidino, and the like.

The term "haloalkyl" denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl, trifluoromethyl, and the like.

The term "alkoxycarbonyl" represents an ester group; i.e. an alkoxy group, attached to the parent molecular moiety through a carbonyl group such as methoxycarbonyl, ethoxycarbonyl, and the like.

The term "thioalkoxy" refers to an alkyl group as previously defined attached to the parent molecular moiety through a sulfur atom.

The term "carboxaldehyde" as used herein refers to a group of formula -CHO.

The term "carboxy" as used herein refers to a group of formula $-CO_2H$.

The term "carboxamide" as used herein refers to a group of formula -CONHR'R" wherein R' and R" are independently selected from hydrogen or alkyl, or R' and R" taken together may optionally be $-(CH_2)_k-$ where k is an integer of from 2 to 6.

The term "heteroaryl", as used herein, refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and the like.

The term "heterocycloalkyl" as used herein, refers to a non-aromatic partially unsaturated or fully saturated 3- to 10-membered ring system, which includes single rings of 3 to 8 atoms in size and bi- or tri-cyclic ring systems which may include aromatic six-membered aryl or heteroaryl rings fused to a non-aromatic ring. These heterocycloalkyl rings include those having from one to three heteroatoms independently selected from oxygen, sulfur and

nitrogen, in which the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized.

Representative heterocycles include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

The term "heteroarylalkyl" as used herein, refers to a heteroaryl group as defined above attached to the parent molecular moiety through an alkylene group wherein the alkylene group is of one to four carbon atoms.

"Hydroxy-protecting group", as used herein, refers to an easily removable group which is known in the art to protect a hydroxyl group against undesirable reaction during synthetic procedures and to be selectively removable. The use of hydroxy-protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, cf., for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991). Examples of hydroxy-protecting groups include, but are not limited to, methylthiomethyl, *tert*-dimethylsilyl, *tert*-butyldiphenylsilyl, ethers such as methoxymethyl, and esters including acetyl benzoyl, and the like.

A the term "protected-hydroxy" refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups, for example.

The term "substituted aryl" as used herein refers to an aryl group as defined herein substituted by independent replacement of one, two or three of the hydrogen atoms thereon with Cl, Br, F, I, OH, CN, C_1-C_3-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy substituted with aryl, haloalkyl, thioalkoxy, amino, alkylamino, dialkylamino, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, any one substitutent may be an aryl, heteroaryl, or heterocycloalkyl group. Also, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "substituted heteroaryl" as used herein refers to a heteroaryl group as defined herein substituted by independent replacement of one, two or three of the hydrogen atoms thereon with Cl, Br, F, I, OH, CN, C_1-C_3-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy substituted with aryl, haloalkyl, thioalkoxy, amino, alkylamino, dialkylamino, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, any one substitutent may be an aryl, heteroaryl, or heterocycloalkyl group.

The term "substituted heterocycloalkyl" as used herein, refers to a heterocycloalkyl group, as defined above, substituted by independent replacement of one, two or three of the hydrogen atoms thereon with Cl, Br, F, I, OH, CN, C_1-C_3-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy substituted with aryl, haloalkyl, thioalkoxy, amino, alkylamino, dialkylamino,

mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, any one substitutent may be an aryl, heteroaryl, or heterocycloalkyl group.

Numerous asymmetric centers may exist in the compounds of the present invention. Except where otherwise noted, the present invention contemplates the various stereoisomers and mixtures thereof. Accordingly, whenever a bond is represented by a wavy line, it is intended that a mixture of stereo-orientations or an individual isomer of assigned or unassigned orientation may be present.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharm. Sci.*, 66: 1-19 (**1977**), incorporated herein by reference. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic,

cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters includes formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or as an oral or nasal spray.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids

such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulations, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

According to the methods of treatment of the present invention, tumors are treated and macular degeneration is treated or prevented in a patient such as a human or lower mammal by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to treat bacterial infections, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the

time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other mammal in single or in divided doses can be in amounts, for example, from 0.01 to 200 mg/kg body weight or more usually from 10 to 100 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 2000 mg of the compound(s) of this invention per day in single or multiple doses.

In a preferred method of the invention of treating tumors and macular degeneration the compound is selected from the group of compounds having the formulas (I) - (V). In a more preferred method the compound is selected from the group of compounds having the formulas:
Compound of Formula (I): R^a = OH, X = NHMe, Y = H, Rc = H;
Compound of Formula (I): R^a = OH, X = NMe_2, Y = H, Rc = Formyl;
Compound of Formula (I): R^a = OH, X and Y taken together form a bond, Rc = H;
Compound of Formula (I): R^a = OH, X = NMe_2, Y = OH, Rc = H;
Compound of Formula (I): R^a = OH, X = NMe(Benzyl), Y = H, Rc = H;
Compound of Formula (II);
Compound of Formula (III): R = $-CH_2CH=CH_2$
Compound of Formula (III): R = $-CH_2CH=N-O-$(Benzyl);
Compound of Formula (III): R = $-CH_3$; (clarithromycin);
Compound of Formula (IV);
Compound of Formula (V): R^a = OH, R^b = H; and
Compound of Formula (V): R^a = OH, R^b = CH_3.

In a preferred pharmaceutical composition of the invention the compound is selected from the group of compounds having the formulas (I) - (V). In a more preferred pharmaceutical composition the compound is selected from the group of compounds listed in the paragraph above.

The foregoing may be better understood by reference to the following examples which are presented for the purpose of illustrating the 6-O-substituted erythromycin derivatives that may be utilized for the treatment of tumors and macular degeneration.

Example 1

In Vitro Anti-Angiogenic Activity of Selected Macrolides

Representative compounds of the present invention were assayed *in vitro* for their ability to induce giant cells in culture of mouse peritoneal macrophages. Since the anti-angiogenic activity of macrolides correlates to their ability to induce giant cells in culture of mouse peritoneal macrophages, the *in vitro* activity of macrolides were determined according to the method described by E. Kita *et al.*, in *Nat. Immun.*, 12, 326-338 (**1993**). The numbers indicate the minimum concentration of analyte necessary to induce giant cells. The data given in Table 1 below indicate that the compounds were effective in inducing giant cells and therefore that the compounds possess anti-angiogenic activity.

Table 1

In Vitro Activity of Selected Compounds*

in Inducing Giant Cells

Compound No.	*Minimum Conc. to Induce (μM)*
1	2.0
2	1.0
3	2.5
4	1.0
5	3.5
6	2.0
7	5.0
8	2.0
11	1.0
12	2.0

* compounds are identified in Table 2 below

Table 2

Identity and Source of Selected Macrolides

Tested by *In Vitro* or *In Vivo* Protocols

Cmpd No.	Compound	Source or method of preparation
1	Compound of Formula (I): R^a = OH, X = NHMe, Y = H, Rc = H	Freiberg, U.S. Patent 3,725,385 (1973)
2	Compound of Formula (I): R^a = OH, X = NMe_2, Y = H, Rc = Formyl	Tanadier *et al.*, *J. Org. Chem.* 39, 2495 (1974)
3	Compound of Formula (I): R^a = OH, X and Y taken together form a bond, Rc = H	Jones and Rowley, *J. Org. Chem.*, 33, 665 (1968)
4	Compound of Formula (I): R^a = OH, X = NMe_2, Y = OH, Rc = H	Jones *et al.*, *Antimicrob. Agents Chemother.*, 123 (1970)
5	Compound of Formula (I): R^a = OH, X = NMe(Benzyl), Y = H, Rc = H	Freiberg, U. S. Patent 3,681,325, issued August 1, 1972
6	Compound of Formula (II)	Kurath *et al.* (*Experientia*, 27, 362 (1971)
7	Compound of Formula (III): R = -$CH_2CH{=}CH_2$	Or *et al.*, disclosed in U.S. Patent Application Serial No. 08/841,038 filed 4/29/97.
8	Compound of Formula (III): R = -CH_2CH=N-O-(Benzyl)	Or *et al.*, disclosed in U.S. Patent Application Serial No. 08/841,038 filed 4/29/97.
9	Compound of Formula (III): R = -CH_3; (clarithromycin)	Abbott Laboratories
10	Compound of Formula (IV)	Hardy *et al.*, *Antimicrob. Agents Chemother.*, 32, 1710-1719 (1988)
11	Compound of Formula (V): R^a = OH, R^b = H	McAlpine *et al.*, *30th Intl. Conf. Antibiot. Agents. Chemother.*, Atlanta, USA, **1990**, Abst. 810
12	Compound of Formula (V): R^a = OH, R^b = CH_3	McAlpine *et al.*, *30th Intl. Conf. Antibiot. Agents. Chemother.*, Atlanta, USA, **1990**, Abst. 810

Example 2

In Vivo Anti-Angiogenic Activity of Selected Macrolides

The anti-angiogenic properties of macrolides were tested *in vivo* in the mouse cornea model. In this model, the neovascularization is induced by bFGF-containing pellet implanted in the cornea. Macrolide was given orally, QD, from day 0 (day of pellet implantation) through day 5. At day 6, mice were perfused with saline and Indian ink. Eyes were removed, fixed and the cornea was isolated, mounted in a glass slide. Microvessel density was determined by image analysis system, and the anti-angiogenic effect the test compound estimated.

Protocols

Pellet preparation. Pellets were prepared which contained a mixture of three substances: 1) Hydron™ (polyhydroxyethylmethacrylate), a slow-release polymer; 2) Sucralfate™, to stabilize and to slow the release of basic fibroblast growth factor (bFGF); and 3) bFGF, a potent angiogenic growth factor. The mixture, after being speed vacuumed and re-suspended into a small volume, was spread onto a sterile nylon mesh. After it is dried, pellets of approximately equal size of 0.4 x 0.4 x 0.2 mm were obtained by pulling apart the fibers of the mesh. Each pellet contains approximately 100 ng of bFGF, an optimal dose established previously.

Pellet implantation. Approximately 8 week old CF-1 albino mice were used in this study. Under anesthesia, and using a dissecting microscope, an intrastromal micropocket was made, at 0.7 mm of the temporal limbus. A single pellet was deposited on the corneal surface and inserted in the pocket. The control animals received no drug treatment. Antibiotic ointment was applied to pellet-implanted eyes immediately after surgery. The eyes were routinely examined postoperatively.

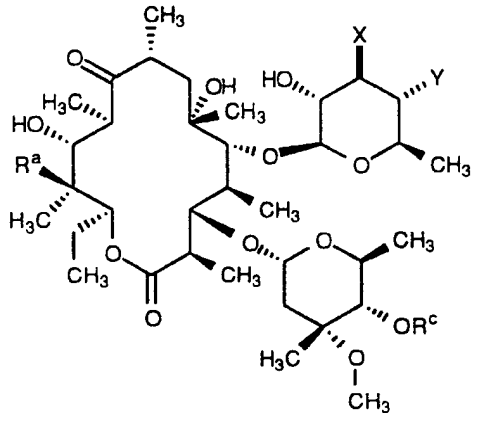
Therapy. Therapy was initiated on day 0, after the mice recovered from anesthesia. In three experiments, compounds were administered orally four times per day to groups of three mice per dose at doses from 25 to 200 mg/kg/day for a period of 6 days. Compound 8 was tested at 100 mg/kg/day, compound 9 was tested at 25 to 200 mg/kg/day, and compound 9 was tested at 100 mg/kg/day. Control groups consisted of three mice per experiment. In two experiments taxol was administered intraperitineally four times per day to groups of three mice per dose at 10 mg/kg/day for 6 days as a toxicity control group.

Examination of Neovascularization. At day 6 postoperative, under deep anesthesia, mice were perfused with an intracardiac injection of about 25 mL of saline, then perfused with an Indian ink 1:30 solution. Eyes were enucleated and fixed with formaldehyde 10% overnight. After fixation, corneas were dissected and mounted onto a glass slide. Microvessel density was measured by image analysis using a Image-Pro Plus™ software program. The microvessel density was measured with arbitrary units and are expressed as mean $\pm$ standard error (n=6).

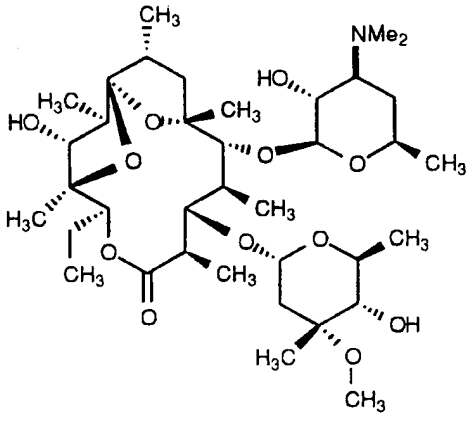
Results. Animals that received taxol had positive signs of toxicity. No signs of gross toxicity were observed in the macrolide treated mice. Compounds 8, 9 and 10 at 100 mg/kg/day decreased angiogenesis by 50% in the mouse cornea model as estimated from the reduced microvessel density in the treated animals.

WHAT IS CLAIMED IS::

1. A method of treating tumors and macular degeneration in a human or veterinary patient comprising administering to a patient a therapeutically effective amount of a compound selected from the group consisting of:



(I),



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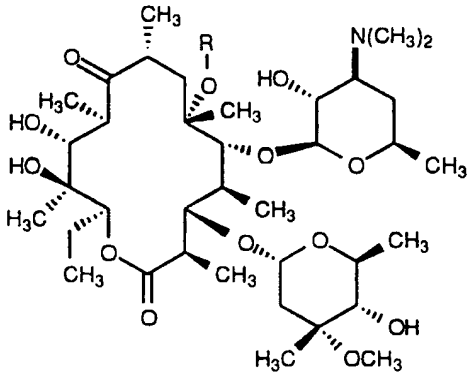
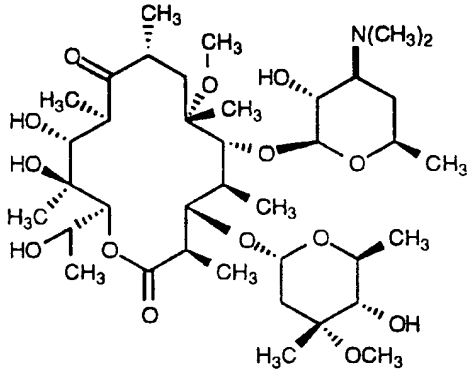
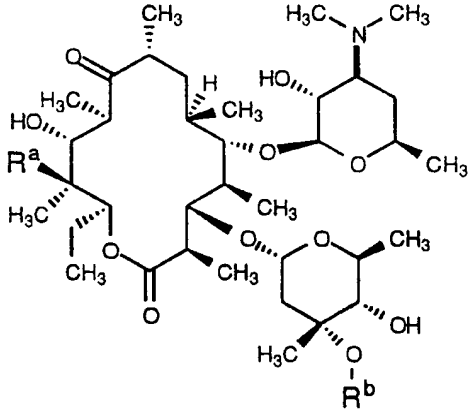
(III),

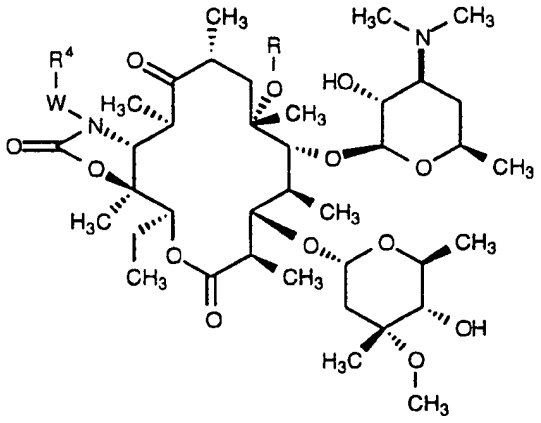


(IV),

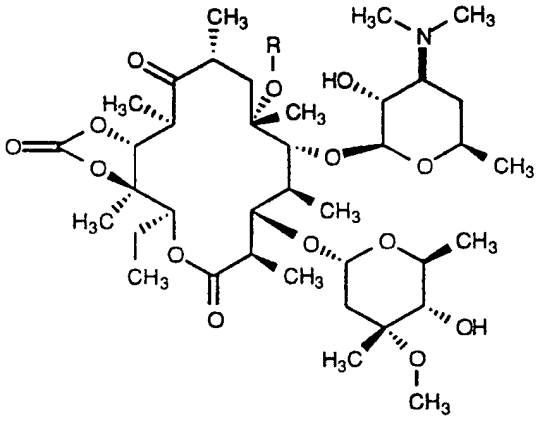


(V),





(VI), , and



(VII),

wherein

R^a is hydrogen or hydroxy;

R^b is hydrogen or methyl;

R^c is hydrogen or hydroxy protecting group;

X is $-NR^1R^2$, wherein R^1 and R^2 are independently selected from

(1) hydrogen, and

(2) C_1-C_3-alkyl optionally substituted with a substituent selected from the group consisting of

(a) aryl,

(b) substituted-aryl,

(c) heteroaryl, and

(d) substituted-heteroaryl,

Y is hydrogen or hydroxyl;

or

X and Y taken together form a bond;

W is absent or is selected from the group consisting of -O-, -NH-, -NH-CO-, and -N=CH:

R^w is selected from the group consisting of

(1) hydrogen,

(2) C_1-C_6-alkyl optionally substituted with one or more substituents selected from the group consisting of

(a) aryl,

(b) substituted-aryl,

(c) heteroaryl,

(d) substituted-heteroaryl,

(e) hydroxy,

(f) C_1-C_6-alkoxy,

(g) NR^1R^2, wherein R^1 and R^2 are as defined previously,

and

(h) $-CH_2-M-R^3$

wherein M is selected from the group consisting of:

(i) -C(O)-NH-,

(ii) -NH-C(O)-,

(iii) -NH-,

(iv) -N=,

(v) $-N(CH_3)-$,

(vi) -NH-C(O)-O-

(vii) -NH-C(O)-NH-

(viii) -O-C(O)-NH-

(ix) -O-C(O)-O-

(x) -O-,

(xi) $-S(O)_n-$, wherein n is 0, 1 or 2,

(xii) -C(O)-O-,

(xiii) -O-C(O)-, and

(xiv) -C(O)-,

and

R^3 is selected from the group consisting of:

(i) C_1-C_6-alkyl, optionally substituted with a substituent selected from the group consisting of

(aa) aryl,

(bb) substituted-aryl,

(cc) heteroaryl, and

(dd) substituted-heteroaryl,

(ii) aryl,
(iii) substituted-aryl,
(iv) heteroaryl,
(v) substituted-heteroaryl, and
(vi) heterocycloalkyl.

(3) C_3-C_7-cycloalkyl,
(4) aryl,
(5) substituted-aryl,
(6) heteroaryl, and
(7) substituted-heteroaryl;

R is selected from the group consisting of

(1) methyl substituted with a moiety selected from the group consisting of
(a) CN,
(b) F,
(c) $-CO_2R^4$ wherein R^4 is selected from the group consisting of C_1-C_3-alkyl, aryl substituted C_1-C_3-alkyl, and heteroaryl substituted C_1-C_3-alkyl,
(d) $S(O)_nR^4$ where n is 0, 1 or 2 and R^4 is as previously defined,
(e) $NHC(O)R^4$ where R^4 is as previously defined,
(f) $NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,
(g) aryl,
(h) substituted aryl,
(i) heteroaryl, and
(j) substituted heteroaryl;
(2) C_2-C_{10}-alkyl;
(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of
(a) halogen,
(b) hydroxy,
(c) C_1-C_3-alkoxy,
(d) C_1-C_3-alkoxy-C_1-C_3-alkoxy,
(e) oxo,
(f) $-N_3$,
(g) -CHO,
(h) O-SO_2-(substituted C_1-C_6-alkyl),
(i) $-NR^5R^6$ wherein R^5 and R^6 are selected from the group consisting of

(i) hydrogen,
(ii) C_1-C_{12}-alkyl,
(iii) substituted C_1-C_{12}-alkyl,
(iv) C_1-C_{12}-alkenyl,
(v) substituted C_1-C_{12}-alkenyl,
(vi) C_1-C_{12}-alkynyl,
(vii) substituted C_1-C_{12}-alkynyl,
(viii) aryl,
(ix) C_3-C_8-cycloalkyl,
(x) substituted C_3-C_8-cycloalkyl,
(xi) substituted aryl,
(xii) heterocycloalkyl,
(xiii) substituted heterocycloalkyl,
(xiv) C_1-C_{12}-alkyl substituted with aryl,
(xv) C_1-C_{12}-alkyl substituted with substituted aryl,
(xvi) C_1-C_{12}-alkyl substituted with heterocycloalkyl,
(xvii) C_1-C_{12}-alkyl substituted with substituted heterocycloalkyl,
(xviii) C_1-C_{12}-alkyl substituted with C_3-C_8-cycloalkyl,
(xix) C_1-C_{12}-alkyl substituted with substituted C_3-C_8-cycloalkyl,
(xx) heteroaryl,
(xxi) substituted heteroaryl,
(xxii) C_1-C_{12}-alkyl substituted with heteroaryl, and
(xxiii) C_1-C_{12}-alkyl substituted with substituted heteroaryl,

or

R^5 and R^6 are taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring which may be substituted with one or more substituents independently selected from the group consisting of

(aa) halogen,
(bb) hydroxy,
(cc) C_1-C_3-alkoxy,
(dd) C_1-C_3-alkoxy-C_1-C_3-alkoxy,
(ee) oxo,
(ff) C_1-C_3-alkyl,
(gg) halo-C_1-C_3-alkyl, and
(hh) C_1-C_3-alkoxy-C_1-C_3-alkyl,

(j) $-CO_2R^4$ wherein R^4 is as previously defined,

(k) $-C(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,

(l) $=N-O-R^4$ wherein R^4 is as previously defined,

(m) -CN,

(n) $O-S(O)_nR^4$ wherein n is 0, 1 or 2 and R^4 is as previously defined,

(o) aryl,

(p) substituted aryl,

(q) heteroaryl,

(r) substituted heteroaryl,

(s) C_3-C_8-cycloalkyl,

(t) substituted C_3-C_8-cycloalkyl,

(u) C_1-C_{12}-alkyl substituted with heteroaryl,

(v) heterocycloalkyl,

(w) substituted heterocycloalkyl,

(x) $NHC(O)R^4$ where R^4 is as previously defined,

(y) $NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,

(z) $=N-NR^5R^6$ wherein R^5 and R^6 are as previously defined,

(aa) $=N-R^3$ wherein R^4 is as previously defined,

(bb) $=N-NHC(O)R^4$ wherein R^4 is as previously defined,

and

(cc) $=N-NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined;

(4) C_3-alkenyl substituted with a moiety selected from the group consisting of

(a) halogen,

(b) -CHO,

(c) $-CO_2R^4$ where R^4 is as previously defined,

(d) $-C(O)-R^3$ where R^3 is as previously defined,

(e) $-C(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,

(f) -CN,

(g) aryl,

(h) substituted aryl,

(i) heteroaryl,

(j) substituted heteroaryl,

(k) C_3-C_7-cycloalkyl,

and

(l) C_1-C_{12}-alkyl substituted with heteroaryl,

(5) C_4-C_{10}-alkenyl;

(6) C_4-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of

(a) halogen,
(b) C_1-C_3-alkoxy,
(c) oxo,
(d) -CHO,
(e) $-CO_2R^4$ where R^4 is as previously defined,
(f) $-C(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,
(g) $-NR^5R^6$ wherein R^5 and R^6 are as previously defined,
(h) $=N-O-R^4$ where R^4 is as previously defined,
(i) -CN,
(j) $O-S(O)_nR^4$ where n is 0, 1 or 2 and R^4 is as previously defined,
(k) aryl,
(l) substituted aryl,
(m) heteroaryl,
(n) substituted heteroaryl,
(o) C_3-C_7-cycloalkyl,
(p) C_1-C_{12}-alkyl substituted with heteroaryl,
(q) $NHC(O)R^4$ where R^4 is as previously defined,
(r) $NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,
(s) $=N-NR^5R^6$ wherein R^5 and R^6 are as previously defined,
(t) $=N-R^3$ wherein R^3 is as previously defined,
(u) $=N-NHC(O)R^4$ where R^4 is as previously defined,
and
(v) $=N-NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined;

(7) C_3-C_{10}-alkynyl;
and
(8) C_3-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of

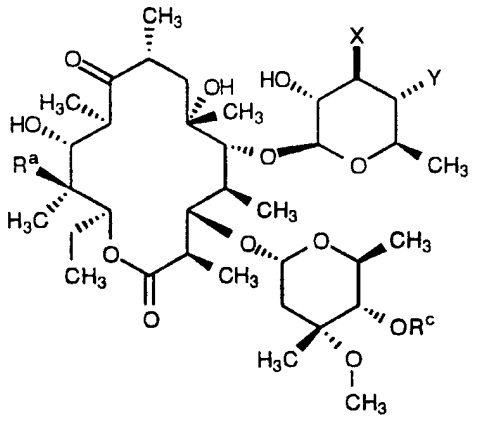
(a) trialkylsilyl,
(b) aryl,
(c) substituted aryl,
(d) heteroaryl,
and
(e) substituted heteroaryl;

in a pharmaceutically acceptable carrier.

2. The method of Claim 1 wherein the compound is selected from the group of compounds having the formulas (I) - (V).

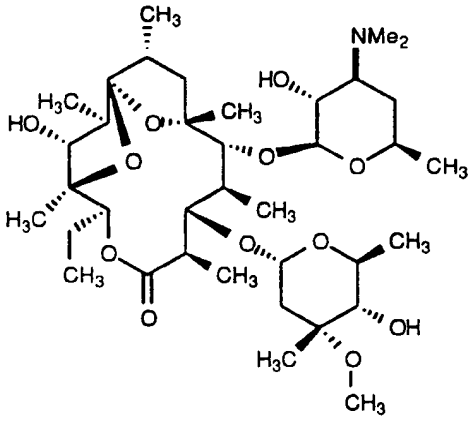
3. The method of Claim 2 wherein the compound is selected from the group of compounds having the formulas:
Compound of Formula (I): R^a = OH, X = NHMe, Y = H, Rc = H;
Compound of Formula (I): R^a = OH, X = NMe_2, Y = H, Rc = Formyl;
Compound of Formula (I): R^a = OH, X and Y taken together form a bond, Rc = H;
Compound of Formula (I): R^a = OH, X = NMe_2, Y = OH, Rc = H;
Compound of Formula (I): R^a = OH, X = NMe(Benzyl), Y = H, Rc = H;
Compound of Formula (II);
Compound of Formula (III): R = $-CH_2CH=CH_2$
Compound of Formula (III): R = $-CH_2CH=N-O-$(Benzyl);
Compound of Formula (III): R = $-CH_3$; (clarithromycin);
Compound of Formula (IV);
Compound of Formula (V): R^a = OH, R^b = H; and
Compound of Formula (V): R^a = OH, R^b = CH_3.

4. A pharmaceutical composition for treating tumors and macular degeneration in a human or veterinary patient comprising a pharmaceutically acceptable carrier and a compound selected from the group consisting of:

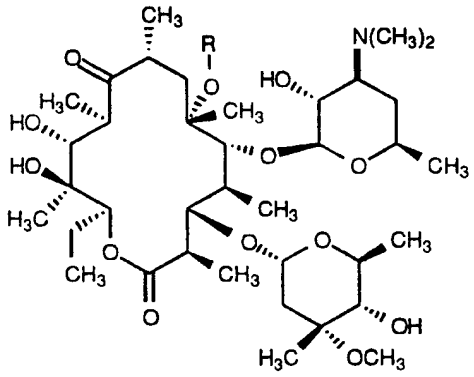


(I),

(II),



(III),



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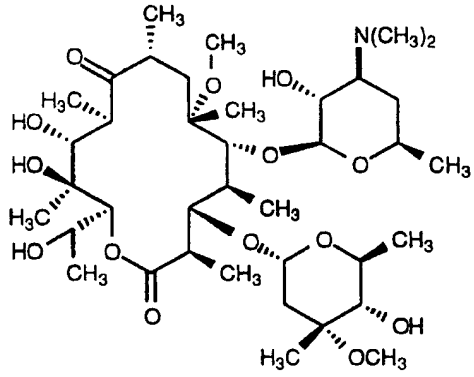
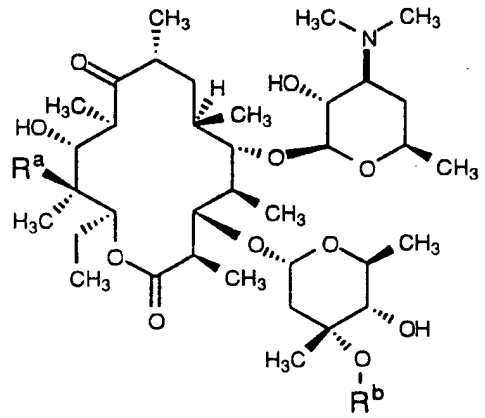
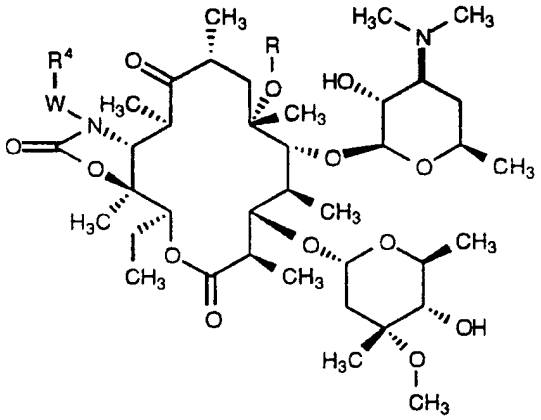
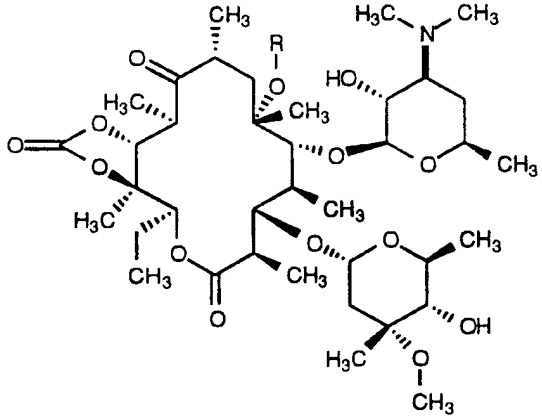




(V),



(VI), , and



(VII),

wherein

R^a is hydrogen or hydroxy;

R^b is hydrogen or methyl;

R^c is hydrogen or hydroxy protecting group;

X is $-NR^1R^2$, wherein R^1 and R^2 are independently selected from

(1) hydrogen, and

(2) C_1-C_3-alkyl optionally substituted with a substituent selected from the group consisting of

(a) aryl,

(b) substituted-aryl,

(c) heteroaryl, and

(d) substituted-heteroaryl,

Y is hydrogen or hydroxyl;

or

X and Y taken together form a bond;

W is absent or is selected from the group consisting of -O-, -NH-, -NH-CO-, and -N=CH;

R^w is selected from the group consisting of

(1) hydrogen,

(2) C_1-C_6-alkyl optionally substituted with one or more substituents selected from the group consisting of

(a) aryl,

(b) substituted-aryl,

(c) heteroaryl,

(d) substituted-heteroaryl,

(e) hydroxy,

(f) C_1-C_6-alkoxy,

(g) NR^1R^2, wherein R^1 and R^2 are as defined previously, and

(h) $-CH_2-M-R^3$

wherein M is selected from the group consisting of:

(i) -C(O)-NH-,

(ii) -NH-C(O)-,

(iii) -NH-,

(iv) -N=,

(v) $-N(CH_3)-$,

(vi) -NH-C(O)-O-

(vii) -NH-C(O)-NH-

(viii) -O-C(O)-NH-

(ix) -O-C(O)-O-

(x) -O-,

(xi) $-S(O)_n-$, wherein n is 0, 1 or 2,

(xii) -C(O)-O-,
(xiii) -O-C(O)-, and
(xiv) -C(O)-,

and

R^3 is selected from the group consisting of:

(i) C_1-C_6-alkyl, optionally substituted with a substituent selected from the group consisting of
(aa) aryl,
(bb) substituted-aryl,
(cc) heteroaryl, and
(dd) substituted-heteroaryl,
(ii) aryl,
(iii) substituted-aryl,
(iv) heteroaryl,
(v) substituted-heteroaryl, and
(vi) heterocycloalkyl,

(3) C_3-C_7-cycloalkyl,
(4) aryl,
(5) substituted-aryl,
(6) heteroaryl, and
(7) substituted-heteroaryl;

R is selected from the group consisting of

(1) methyl substituted with a moiety selected from the group consisting of
(a) CN,
(b) F,
(c) $-CO_2R^4$ wherein R^4 is selected from the group consisting of C_1-C_3-alkyl, aryl substituted C_1-C_3-alkyl, and heteroaryl substituted C_1-C_3-alkyl,
(d) $S(O)_nR^4$ where n is 0, 1 or 2 and R^4 is as previously defined,
(e) $NHC(O)R^4$ where R^4 is as previously defined,
(f) $NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,
(g) aryl,
(h) substituted aryl,
(i) heteroaryl, and
(j) substituted heteroaryl;
(2) C_2-C_{10}-alkyl;

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) C_1-C_3-alkoxy-C_1-C_3-alkoxy,

(e) oxo,

(f) $-N_3$,

(g) -CHO,

(h) O-SO_2-(substituted C_1-C_6-alkyl),

(i) $-NR^5R^6$ wherein R^5 and R^6 are selected from the group consisting of

(i) hydrogen,

(ii) C_1-C_{12}-alkyl,

(iii) substituted C_1-C_{12}-alkyl,

(iv) C_1-C_{12}-alkenyl,

(v) substituted C_1-C_{12}-alkenyl,

(vi) C_1-C_{12}-alkynyl,

(vii) substituted C_1-C_{12}-alkynyl,

(viii) aryl,

(ix) C_3-C_8-cycloalkyl,

(x) substituted C_3-C_8-cycloalkyl,

(xi) substituted aryl,

(xii) heterocycloalkyl,

(xiii) substituted heterocycloalkyl,

(xiv) C_1-C_{12}-alkyl substituted with aryl,

(xv) C_1-C_{12}-alkyl substituted with substituted aryl,

(xvi) C_1-C_{12}-alkyl substituted with heterocycloalkyl,

(xvii) C_1-C_{12}-alkyl substituted with substituted heterocycloalkyl,

(xviii) C_1-C_{12}-alkyl substituted with C_3-C_8-cycloalkyl,

(xix) C_1-C_{12}-alkyl substituted with substituted C_3-C_8-cycloalkyl,

(xx) heteroaryl,

(xxi) substituted heteroaryl,

(xxii) C_1-C_{12}-alkyl substituted with heteroaryl, and

(xxiii) C_1-C_{12}-alkyl substituted with substituted heteroaryl,

or

R^5 and R^6 are taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring which may be substituted with one or more substituents independently selected from the group consisting of

(aa) halogen,
(bb) hydroxy,
(cc) C_1-C_3-alkoxy,
(dd) C_1-C_3-alkoxy-C_1-C_3-alkoxy,
(ee) oxo,
(ff) C_1-C_3-alkyl,
(gg) halo-C_1-C_3-alkyl, and
(hh) C_1-C_3-alkoxy-C_1-C_3-alkyl,

(j) $-CO_2R^4$ wherein R^4 is as previously defined,
(k) $-C(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,
(l) $=N-O-R^4$ wherein R^4 is as previously defined,
(m) -CN,
(n) $O-S(O)_nR^4$ wherein n is 0, 1 or 2 and R^4 is as previously defined,
(o) aryl,
(p) substituted aryl,
(q) heteroaryl,
(r) substituted heteroaryl,
(s) C_3-C_8-cycloalkyl,
(t) substituted C_3-C_8-cycloalkyl,
(u) C_1-C_{12}-alkyl substituted with heteroaryl,
(v) heterocycloalkyl,
(w) substituted heterocycloalkyl,
(x) $NHC(O)R^4$ where R^4 is as previously defined,
(y) $NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,
(z) $=N-NR^5R^6$ wherein R^5 and R^6 are as previously defined,
(aa) $=N-R^3$ wherein R^4 is as previously defined,
(bb) $=N-NHC(O)R^4$ wherein R^4 is as previously defined,
and
(cc) $=N-NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined;

(4) C_3-alkenyl substituted with a moiety selected from the group consisting of

(a) halogen,
(b) -CHO,

(c) $-CO_2R^4$ where R^4 is as previously defined,
(d) $-C(O)-R^3$ where R^3 is as previously defined,
(e) $-C(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,
(f) -CN,
(g) aryl,
(h) substituted aryl,
(i) heteroaryl,
(j) substituted heteroaryl,
(k) C_3-C_7-cycloalkyl,
and
(l) C_1-C_{12}-alkyl substituted with heteroaryl,

(5) C_4-C_{10}-alkenyl;

(6) C_4-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of
(a) halogen,
(b) C_1-C_3-alkoxy,
(c) oxo,
(d) -CHO,
(e) $-CO_2R^4$ where R^4 is as previously defined,
(f) $-C(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,
(g) $-NR^5R^6$ wherein R^5 and R^6 are as previously defined,
(h) $=N-O-R^4$ where R^4 is as previously defined,
(i) -CN,
(j) $O-S(O)_nR^4$ where n is 0, 1 or 2 and R^4 is as previously defined,
(k) aryl,
(l) substituted aryl,
(m) heteroaryl,
(n) substituted heteroaryl,
(o) C_3-C_7-cycloalkyl,
(p) C_1-C_{12}-alkyl substituted with heteroaryl,
(q) $NHC(O)R^4$ where R^4 is as previously defined,
(r) $NHC(O)NR^1R^2$ wherein R^1 and R^2 are as previously defined,
(s) $=N-NR^5R^6$ wherein R^5 and R^6 are as previously defined,
(t) $=N-R^3$ wherein R^3 is as previously defined,
(u) $=N-NHC(O)R^4$ where R^4 is as previously defined,
and

(v) =N-NHC(O)NR^{1}R^2 wherein R^1 and R^2 are as previously defined:

(7) C_3-C_{10}-alkynyl;

and

(8) C_3-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of

(a) trialkylsilyl,

(b) aryl,

(c) substituted aryl,

(d) heteroaryl,

and

(e) substituted heteroaryl.

5. The pharmaceutical composition of Claim 4 wherein the compound is selected from the group of compounds having the formulas (I) - (V).

6. The pharmaceutical composition of Claim 5 wherein the compound is selected from the group of compounds having the formulas:

Compound of Formula (I): R^a = OH, X = NHMe, Y = H, Rc = H;

Compound of Formula (I): R^a = OH, X = NMe_2, Y = H, Rc = Formyl;

Compound of Formula (I): R^a = OH, X and Y taken together form a bond, Rc = H;

Compound of Formula (I): R^a = OH, X = NMe_2, Y = OH, Rc = H;

Compound of Formula (I): R^a = OH, X = NMe(Benzyl), Y = H, Rc = H;

Compound of Formula (II);

Compound of Formula (III): R = -CH_2CH=CH_2

Compound of Formula (III): R = -CH_2CH=N-O-(Benzyl);

Compound of Formula (III): R = -CH_3; (clarithromycin);

Compound of Formula (IV);

Compound of Formula (V): R^a = OH, R^b = H; and

Compound of Formula (V): R^a = OH, R^b = CH_3.